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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	PAPER NUMBER
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,365	BOOM ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74-128* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *115-117 and 121-123* is/are allowed.

6)☒ Claim(s) *74-114,118-120 and 124-128* is/are rejected.

7)☒ Claim(s) *109-111 and 124* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/05/2007 has been entered.

Status

Claims 74-128 are pending in the application. All claims are newly added; all previous claims have been cancelled. Accordingly, there are no pending rejections and all rejections set forth below are new.

Claim Interpretation

Claim 74 recites a step (c)*: generating one or more compomer witnesses corresponding to each different fragment identified in (b)*. This is also recited in claim 115 step (e): *generating from the spectrum of different fragments of (d) one or more compomer witnesses corresponding to each of the different fragments*. In order to construe what this means, the specification was consulted. At paragraph [0024] of the published application, it is stated (with emphasis provided by the examiner):

> Once the masses of the fragments corresponding to differences between the target sequence and the reference sequence are determined ("different" fragments), <u>one or more nucleic acid base compositions (compomers) are identified whose masses differ from the actual measured mass of each different fragment by a value that is less than or equal to a sufficiently small mass difference</u>. These compomers are called witness compomers. The value of this sufficiently small mass difference is determined by parameters such as, <u>but not limited to</u>…

In other words, a “witness compomer” is a base composition for which the predicted mass is within a “sufficiently small mass difference” from the actual measured mass of the fragment that is different. However, since "sufficiently small mass difference" is not defined or limited, *any* compomer can be considered a "witness compomer". Hence, the step of generating one or more witness compomers is simply deducing one or more compomers (base compositions) for which the calculated or predicted mass fits the observed mass, unless otherwise limited by the claim.

Claim 74 also recites a step (d): *identifying a reduced set of candidate sequence variations corresponding to the compomer witnesses, whereby the one or more sequence variations in the target nucleic acid are determined from the candidate sequence variations.* Claim 115 recites this act in steps (f) and (h), with an intermediate step (g): *scoring the candidate sequences of (f)*. Again, the specification was consulted in order to construe these limitations. At paragraph [0123] of the published application, it is stated:

> As used herein, a reduced set of sequence variation candidates refers to a subset of all possible sequence variations in the target sequence that would generate a given set of fragments upon specific cleavage of the target sequence.

As far as the examiner can ascertain, this means that a “reduced set of sequence variation candidates” is a set of possible sequences that would generate a fragment pattern consistent with that actually observed. Hence, this limitation is construed to mean deducing one or more sequences that are consistent with the observed fragment (mass) pattern.

Claim Objections

Claim 124 is objected to because of the following informalities: it would appear that C.sub.k recited in steps (c), (e) and the fourth from the last line of the claim should be C_k. Similarly, "store" in steps (c) and (d) should be "storing". Also, .ltoreq. found repeatedly in the last four lines of the claim should be ≤. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 106-108 and 118-120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 106 and 118 (and by dependency claims 107, 108, 119 and 120) recite "one or more reference sequences having at most k sequence variations". This is unclear because the reference sequence, by definition, would not have variations. It would presumably be the target sequence or the sequence variation candidates that would have at most k sequence variations (*relative* to the reference sequence(s)). Additionally, if there are multiple reference sequences, assuming these multiple reference sequences are not identical to one another, it is unclear what "k sequence variations" means. Would this mean "k sequence variations" relative to any *one* of the reference sequences? If there are two different reference sequences, but each reference sequence has a "G" at position 17, whereas the target has a "T" at position 17, does this count as two sequence variations or only one?

Claims 124-128 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 124 (and by dependency claims 125-128) recites in step (a) "whether modified nucleotides or amino acids are incorporated into all or part of *the sequence*". It is unclear whether "the sequence" refers to the reference sequence or to the target nucleic acid sequence being analyzed.

Also in step (a), it is unclear what "different fragments" refers to. Are these different fragments of the reference sequence *s* resulting from the cleavage reaction conditions? Or does this refer to the fragments that differ between the target sequence and reference sequence *s*?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 74-83, 85-91, 94-102, 105, 113 and 114 are rejected under 35 U.S.C. 102(b) as being anticipated by Foote et al (WO 98/54571, cited on the IDS of 7/27/2004).

With regard to claims 74 and 85, Foote teaches a method comprising:

(a) providing mass signals of fragments resulting from (i) specific cleavage of a target nucleic acid and a reference nucleic acid into fragments, and (ii) determining mass signals of the fragments (page 4, lines 10-20; page 9, lines 1-14);

(b) identifying differences in mass signals between target nucleic acid fragments and reference nucleic acid fragments, thereby identifying different fragments (page 4, lines 10-20; page 9, lines 1-14);

(c) generating one or more compomer witnesses corresponding to each different fragment identified in (b) (page 9, line 25 through page 10, line 1: "…allowing unambiguous assignation of base composition to each oligonucleotide."); *and*

(d) identifying a reduced set of candidate sequence variations corresponding to the compomer witnesses, whereby the one or more sequence variations in the target nucleic acid are determined from the candidate sequence variations (page 9, line 25 through page 10, line 1: "This knowledge allows deduction of the nature of the mutation and, after specific cleavage at different bases and integration of the data, the position of the mutation.").

Since Foote teaches assigning base composition (i.e. compomer) to each oligonucleotide, this qualifies as generating a compomer witness. As the claims are silent with regard as to *how* a reduced set of candidate sequence variations is identified, Foote's method of carrying out further specific cleavages and integrating the data in order to arrive at the nature and position of the nucleotide variation qualifies as identifying a reduced set of sequence variation candidates, whereby the one or more sequence variations in the target nucleic acid are determined.

With regard to claim 75, Foote teaches at page 9, lines 11-13: "Consequently, any nucleotide substitution results in either a shifted peak due to the mass difference in the new cleavage fragment or, if the mutation changes the targeted base, a cleavage product containing a different number of bases." Since Foote is conducting base-specific cleavage, what this means, and what one of ordinary skill in the art would have understood, is that a "shifted peak" represents both a "missing signal" relative to the reference sequence, as well as a corresponding "additional signal". In the case described by Foote where the nucleotide substitution changes the targeted base (i.e. the base at which cleavage occurs), this would also result in one or more "missing" and corresponding "additional" signals.

With regard to claims 76 and 99, Foote teaches mass spectrometry (e.g. page 9, lines 5-6).

With regard to claims 77-81, Foote teaches at page 9, lines 15-17: "…detecting a difference of one or more nucleotides between a nucleic acid molecule to be tested and a reference nucleic acid molecule…". The term "more" in this context must be at least two, since one cannot have a "half" nucleotide. Since each of these two or more nucleotide differences can be regarded as a separate sequence variation, even if the two or more nucleotide differences are immediately adjacent, the limitations of claim 77 are met. Foote also teaches the method is able to detect point mutations (i.e. single nucleotide polymorphisms or substitutions) and insertions/deletions (page 20, lines 25-31).

With regard to claims 82 and 83, Foote teaches his method "has applications in polymorphism analysis of populations and in studies of evolution, drug resistance, virulence or attenuation of disease agents such as bacteria, viruses or protozoa" (page 12, lines 4-6).

With regard to claims 86-89 and 95, Foote teaches an embodiment in which nucleic acid samples from 9 individuals heterozygous for a polymorphism in the IL-12 gene were pooled (page 27, lines 7-8). Since one allele can be considered the "reference" for the other allele, such pooled samples represent a mixture comprising multiple targets and multiple reference sequences.

With regard to claims 90, 91 and 94, Foote teaches base-specific cleavage of the target and reference, with optional further base-specific cleavage of different bases (see entire page 9). In one embodiment, Foote teaches using a glycosylase for this cleavage (page 11, lines 8-10).

With regard to claims 96 and 102, Foote teaches the method may be used for "diagnosis of a suspected disease" (page 12, lines 1-5). One of skill in the art would have understood this to mean the nucleic acid is from a single individual, since it was not generally practiced in the art to render diagnosis using nucleic acid pooled from different individuals. Foote teaches genomic DNA (page 10, lines 3-7).

With regard to claim 97, Foote teaches at page 10, lines 3-7: "…DNA, genomic DNA, cDNA, plasmid DNA, satalite [sic] DNA, mRNA and other RNA molecules as well as DNA:DNA, DNA:RNA and RNA:RNA hybrids."

With regard to claim 98, Foote teaches mRNA (page 10, lines 3-7), which is produced by transcription.

With regard to claims 100 and 101, Foote teaches simulated cleavage (page 29, last paragraph). Foote also teaches at page 12, lines 10-13: "Alternatively, the wild-type nucleic acid molecule may already have been analysed. Conveniently, this information may be stored electronically and upon completion of the analysis of the test nucleic acid molecule, both the test and reference sequences may then be compared manually, electronically or by a computer assisted means." This can be construed as an electronic simulation of the cleavage of the reference nucleic acid.

With regard to claim 105, Foote teaches assigning base composition (compomer) on the bases of mass (page 9, lines 29-30).

With regard to claims 113 and 114, since Foote teaches unambiguously assigning a base composition to each oligonucleotide fragment based on its mass, it is submitted that such base composition qualifies as a "witness" compomer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 112 is rejected under 35 U.S.C. 103(a) as being unpatentable over Foote et al (WO 98/54571, cited on the IDS of 7/27/2004).

The teachings of Foote have been discussed.

Foote does not teach recording the sequence variation in the target nucleic acid in a record.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to record the results of the analysis in a record, so that one would not have to either remember the results indefinitely or else repeat the analysis every time one needed to know the result.

Claims 84, 92, 93 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foote et al (WO 98/54571, cited on the IDS of 7/27/2004) in view of Zabeau et al (WO 00/66771, cited on the IDS of 04/18/2006).

The teachings of Foote have been discussed.

Foote does not teach applying the method to one of the recited bacteria in claim 84.

Foote does not teach using RNase as the base-specific cleavage agent (as recited in claim 92) or the specific RNases recited in claim 93.

Foote teaches applying his method to screening for cancer (page 12, line 2), but does not specifically teach using nucleic acid from a tumor as recited in claim 104.

Zabeau teaches a method similar to, but expanding upon, that of Foote. For example, Zabeau teaches at page 7, lines 13-21:

> In one embodiment, the present invention is directed to methods for sequence analysis of one or more target nucleic acids for which a known reference nucleic acid sequence is available. In this method, one or more target nucleic acids are derived from one or more biological samples, and a reference nucleic acid are each subjected to complementary cleavage reactions, and the products of the cleavage reactions are analyzed by mass spectroscopic methods. The mass spectra of the one or more target nucleic acids are then compared with the mass spectra of the reference nucleic acid sequence, and the nucleotide sequence of the one or more target nucleic acids is deduced by systematic computational analysis.

With regard to claim 84, Zabeau teaches his method can be applied to detecting sequence variations in *Mycobacterium tuberculosis* (see page 36, lines 4-6).

With regard to claims 92 and 93, Zabeau teaches G-specific T_1 ribonuclease, the A-specific U_2 ribonuclease, the A/U specific phyM ribonuclease, the U/C specific ribonuclease A, the C-specific chicken liver ribonuclease (RNaseCL3), and cusativin (page 9, lines 18-21).

With regard to claim 104, Zabeau teaches analysis of nucleic acid from tumor samples (page 6 lines 5-7).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to apply the method taught by Foote to *Mycobacterium tuberculosis* or tumor samples, and to use the base specific cleavage agents taught by Zabeau, since such applications and reagents were already known in the art for use in

the method of Zabeau, which was virtually indistinguishable from the method taught by Foote.

Claim 103 is rejected under 35 U.S.C. 103(a) as being unpatentable over Foote et al (WO 98/54571, cited on the IDS of 7/27/2004) in view of Muller et al (Human Molecular Genetics, vol 9, no 5, pp 757-763, 2000, prior art of record).

The teachings of Foote have been discussed.

Foote does not teach using the method to determine epigenetic changes in a target nucleic acid as recited in claim 103.

Muller teaches the use of a mass-spectrometry-based method for analyzing the imprinting status of the *TSSC3* gene (see page 757, column 2, penultimate paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to apply the method of Foote to the analysis of imprinting status as taught by Muller, because, as Muller states on page 757, 1st sentence of the *Introduction*, "Epigenetic alterations to gene function are important in tumorigenesis". Therefore, one would have been motivated to substitute use Foote's method to assess epigenetic changes.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 74-123 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 17-19, 21-26, 28-31 and 42 of copending Application No. 10/933,611. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the '611 application only differ from the instant claims in that they are more specific by way of reciting how the nucleic acid is prepared prior to base-specific fragmentation, mass spec analysis, identification of fragments that differ between the target and reference sequence, generation of compomer witnesses, and scoring sequence variation candidates. Thus the claims of the '611 application represent a species which anticipates the more generic claims of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

Claims 109-111 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 115-117 and 121-123 are allowed.

The closest prior art is found in the disclosures of Foote and Zabeau discussed above. However, these prior art methods teach how to deduce the actual sequence of the variant nucleic acid through a process of elimination by performing a series of base-specific cleavage reactions. Since these prior art methods arrive at the actual sequence (which is nonetheless a "reduced set of sequence variation candidates"), there would have been no reason to "score" the sequence variation candidates (as recited in claim 115, step (g)) or using an algorithm such as that recited in claim 124 to predict the sequence variation. As per paragraph [0125] of the published application, “scoring or a score refers to a calculation of the probability that a particular sequence variation candidate is actually present in the target nucleic acid or protein sequence”. There would have been no reason to modify the teachings of Foote or Zabeau to do this, since these prior art methods teach how to experimentally obtain the actual sequence.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

scw

/Young J Kim/
Primary Examiner, Art Unit 1637